severe necrotizing pancreatitis and early operative or catheter drainage may result in improved survival rates. The use of prophylactic antibiotics in these patients should be evaluated by a controlled trial.

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REFERENCES

Beger HG, Bittner R, Block S, et al: Bacterial contamination of pancreatic necrosis—A prospective clinical study. Gastroenterology 1986; 91:433-438

Gerzof SG, Banks PA, Robbins AH, et al: Early diagnosis of pancreatic infection by computed tomography-guided aspiration. Gastroenterology 1987; 93:1315-1320

Nordestgaard AG, Wilson SE, Williams RA: Early computerized tomography as a predictor of outcome in acute pancreatitis. Am J Surg 1986; 152:127-132

Ventrucci M, Pezzilli R, Gullo L, et al: Role of serum pancreatic enzyme assays in diagnosis of pancreatic disease. Dig Dis Sci 1989; 34:39-45

Misoprostol Therapy for Patients Taking Nonsteroidal Anti-inflammatory Drugs

GASTROPATHY INDUCED BY the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is a major complication of these widely prescribed drugs. Patients at highest risk for gastropathy are those on long-term NSAID therapy, including the elderly, arthritic patients, and those with a history of abdominal pain or gastric intolerance to NSAIDs. The spectrum of gastropathy includes mucosal hemorrhages or erosions, gastric ulcer—present in as many as 15% of the population at risk—and duodenal ulcer, and any of these may present with complications such as gastrointestinal bleeding or perforation. Attempts to prevent NSAID-related gastropathy with H_2-receptor blockers and sucralfate have been unsuccessful, though these agents remain useful for healing established ulcers once NSAID therapy is discontinued.

The mechanism of NSAID-induced mucosal damage is not completely understood. The suppression of mucosal prostaglandin production and a reduction of mucosal blood flow by NSAIDs are contributing factors, and the presence of gastric acid is required. Prostaglandins such as misoprostol, a synthetic prostaglandin E_2 analogue, have been investigated for their role in gastric mucosal protection, particularly against insults such as from taking NSAIDs. In low doses these agents have cytoprotective properties such as enhancing mucosal blood flow and gastric mucous production. In higher doses they can inhibit gastric acid secretion. In healthy subjects misoprostol use has been shown to prevent mucosal lesions induced by NSAIDs and aspirin. Even with doses below antisecretory levels, patients had lowered endoscopic scores of mucosal damage, suggesting cytoprotection by misoprostol. Notably, abdominal pain and other gastrointestinal symptoms were not reduced in these short-term studies.

Two recent trials show the clinical usefulness of misoprostol in arthritic patients on NSAID therapy. One trial enrolled patients with abdominal pain but without gastric ulcers on endoscopy and showed a significantly reduced incidence of gastric ulcer in the group treated with misoprostol. Because the overall incidence of gastric ulcer was high, the study was terminated for ethical reasons before statistically significant data could be collected on the effects on duodenal ulcers. In a second study, misoprostol therapy produced substantial regression of gastropathy in patients with rheumatoid arthritis who continued on aspirin therapy. No exacerbation of arthritic symptoms was noted in patients treated with misoprostol.

Unfortunately, none of these studies have shown any consistent benefit on abdominal symptoms; in fact, some have shown worsened gastrointestinal symptoms in the misoprostol-treated patients. This is due in part to the side effects of the drug, which include diarrhea, dyspepsia, and abdominal pain, and may require reducing the dose from the recommended starting dose of 200 μg four times a day to 100 μg. Misoprostol also has uterotonic effects and may cause cramping, bleeding, or spontaneous abortion, necessitating extreme caution in prescribing to women of childbearing age and contraindicating its use in pregnancy.

Misoprostol therapy should certainly be considered for patients with disabling arthritis who need to continue on NSAID therapy despite a serious complication—such as gastric ulcer or gastrointestinal bleeding—from these agents. It may be indicated in symptomatic patients on NSAID therapy, particularly elderly or chronically ill persons, to prevent the development of gastric complications. Because its efficacy in reducing symptoms has not been shown, assessing any clinical benefit over the short term may be difficult, especially because many of these patients will not be followed up with endoscopy. The role of misoprostol therapy in high-risk asymptomatic patients without documented gastrointestinal complications bears further investigation. Its effects on the prevention and healing of duodenal ulcers need to be assessed. Finally, long-term studies are needed to evaluate the efficacy of misoprostol therapy in preventing more serious complications such as gastrointestinal bleeding and perforation and to identify the patient groups that may benefit from such therapy.

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REFERENCES

Fries JF, Miller SR, Spitz PW, et al: Toward an epidemiology of gastropathy associated with nonsteroidal antiinflammatory drug use. Gastroenterology 1989; 96 (Pt 2 suppl):647-655

Graham DY, Agrawal NM, Roth SH: Prevention of NSAID-induced gastric ulcer with misoprostol: Multicentre, double-blind, placebo-controlled trial. Lancet 1988; 2:1277-1280

Roth S, Agrawal N, Mahowald M, et al: Misoprostol heals gastroduodenal injury in patients with rheumatoid arthritis receiving aspirin. Arch Intern Med 1989; 149:775-779

Stern WR: Summary of the 33rd Meeting of the Food and Drug Administration's Gastrointestinal Drugs Advisory Committee, September 15-16, 1988. Am J Gastroenterol 1989; 84:351-353

Rheumatoid Arthritis and Methotrexate—A Renewed Partnership

METHOTREXATE was first used to treat hematologic malignant disorders in the late 1940s. It was later tried in rheumatic diseases with the assumption that the two groups of patients shared a similar pathophysiology. Because of the serious side effects associated with the earlier dosage regimens and the recognition of the dramatic effects of corticosteroids, its use was soon discarded. The modern application of methotrexate began in the 1960s when introduced in the treatment of psoriasis and dermatomyositis.

Since 1980 when an eight-year experience with the use of methotrexate to treat rheumatoid arthritis was described, several authors have published data supporting the relative safety and efficacy of its use in patients with this disorder. In 1988 the American College of Physicians published a "position paper" describing its use, and this year, after 45 years on the market, the Food and Drug Administration approved its use for the treatment of rheumatoid arthritis.

Methotrexate is a folic acid analogue. It inactivates intracellular enzymes, depleting the cell of reduced folates necessary for the formation of purines and pyrimidines and thus DNA. Its mechanism of action in rheumatoid arthritis is un-